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(21) International Application Number: PCT/EP97/04740 (22) International Filing Date: 1 September 1997 (01.09.97) (30) Priority Data: 60/025,990 12 September 1996 (12.09.96) US 60/043,228 10 April 1997 (10.04.97) US (71) Applicant: ASTA MEDICA AKTIENGESELLSCHAFT [DE/DE]; An der Pikardie 10, D-01277 Dresden (DE). (72) Inventors: ENGEL, Jürgen ; Erlenweg 3, D-63755 Alzenau (DE). REISSMANN, Thomas ; Massbornstrasse 44, D-60347 Frankfurt (DE). RIETHMÜLLER-WINZEN, Hilde ; Mittelweg 27, D-60318 Frankfurt (DE). RAWERT, Jürgen ; Bezirksstrasse 27, D-63755 Alzenau (DE).	(81) Designated States: AU, BR, CN, CZ, EE, HU, IL, IS, JP, KR, LT, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: MEANS FOR TREATING PROSTATE HYPERTROPHY AND PROSTATE CANCER (57) Abstract A regime for therapeutic management of a benign prostatic hyperplasia and prostatic cancer employs Cetrorelix alone or in combination with α -reductase inhibitors or α -receptor blocking agents. The regimen reduces the volume of the prostate and avoids the side effects associated with testosterone levels being in a castration range. Cetrorelix is administered at dosages between 0.5 mg/day and 20 mg/week or about 0.014 mg/kg body weight per day to 0.30 mg/kg body weight per week or at levels of about 25 to 120 mg of Cetrorelix per month or 0.376 mg/kg to 1.71 mg/kg per month. Cetrorelix can be administered with α -reductase inhibitors or α -receptor blocking agents.		

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MEANS FOR TREATING PROSTATE HYPERTROPHY
AND PROSTATE CANCER

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION:

The invention is related to a method of treating benign prostate hypertrophy (BPH) and prostate cancer as well as to means of use therefor.

DESCRIPTION OF RELATED ART

BPH is a disease conditioned by age and affects approximately 60 % of all men older than 60. Pathogenetically, an elevated accumulation of dihydrotestosterone in the prostate tissue is assumed to cause enlargement of the prostate. The accumulation of dihydrotestosterone is thought to be the result of elevated intracellular bonding based on receptor increase. The increase in receptors is stimulated by the elevation of the estrogen levels relative to androgen levels which decrease with age. The urological symptoms consist in an elevated frequency of miction due to elevated residual urine, which bothers the patients especially during the night hours. This is accompanied by a weak flow of urine, a time-delayed start of miction, and repeated infections of the bladder and kidneys.

Surgical elimination of the obstruction due to prostate enlargement is still considered the "gold standard" within the various modalities of treatment. Surgery, however, is not

effective for all patients. Open operation or a transurethral resection results in no improvement in approximately 10 to 15 % of the patients due to the presence of other causes, e.g. neurogenic bladder, infections. In addition, these invasive methods entail additional risks such as the occurrence of a retrograde ejaculation, diminished libido and urine incontinence. Less invasive methods exist, e.g. balloon dilatation and treatment with hyperthermia or microwaves.

It has been established that an androgen-ablative therapy can yield positive results in the case of BPH; however, it is unclear whether full suppression should be achieved. The standard therapy for testosterone suppression in the case of prostate carcinomas consists in a bilateral orchiectomy. This is not generally acceptable for a benign sickness such as BPH. Another possibility involves influencing the effects of the sexual steroids through the use of LHRH analogues (LHRH = luteinizing hormone-releasing hormone).

After an initial stimulation of the steroid, the use of "superagonists" causes suppression of testosterone at castration levels. The stimulation is due to their mechanism of action. Unfortunately, the use of "superagonists" has the same undesirable side effects associated with surgical castration.

Dyssynergia α -receptor blockers can be used in the case of a rigid sphincter or bladder sphincter. Alternative drug regimens involve the use of 5- α -reductase inhibitors such as

Finasteride to inhibit the formation of dihydrotestosterone. This regimen has the additional advantage of not negatively influencing the libido or potency.

EP 0.401,653 teaches the use of Naftopidil for therapy of dysuria in BPH (oral daily 10 - 100 mg). Dysuria is discussed in the background section.

WO publication 91/100731 describes a combination therapy for the prophylaxis or treatment of BPH by the combined administration of 2 or more therapeutic substances. The substances are selected from the group of 5- α -reductase inhibitors, anti-estrogens, aromatase inhibitors, inhibitors of 17 β -hydroxysteroid dehydrogenase activity and, in a few instances, of anti-androgens and/or LHRH agonists / antagonists. The anti-androgens were preferably given 2 to 4 hours before the administration of the LHRH agonist.

WO publication 91/00733 teaches the treatment of androgen-dependent diseases with a new anti-androgen which can also be used in the context of a combination therapy. The treatment includes the steps of inhibiting the testicular hormonal secretion by administering an antagonist of LHRH or an agonist of LHRH along with a pharmaceutically effective amount of an anti-androgen.

WO publication 92/16233 describes the combined use of an inhibitor of 5- α -reductase and an anti-androgen for the treatment of prostate cancer. The combination of Finasteride with an anti-

androgen, e.g. Flutamide, is also taught. The use of a composition of various LHRH agonists and of an anti-androgen for treating BPH is also suggested by US 4,472,382.

WO publication 92/16213 teaches a method of treating BPH by administering an inhibitor of 5- α -reductase select from 17 β -substituted 4-azasteroid, 17 β -substituted non-azasteroid, 17 β -acetyl-3-carboxy-androst-3,6-diene together with an α^1 adrenergic receptor blocker selected from Terazosin, Doxazosin, Prazosin, Bunazosin, Indoramin, Alfuzosin.

The use of the LHRH antagonist Cetrorelix (SB 75), (see also EP 0299 402), for treating BPH is suggested in "The Prostate" 24:84 92 (1994), (Gonzalez-Barcena et al). Gonzalez-Barcena et al report desirable clinical results, e.g. a decrease in prostate volume, after the administration of 500 μ g Cetrorelix (SB-075) every 12 hours for 4 weeks to BPH patients. Prostate carcinoma patients were also similarly treated for 6 weeks. In all patients, there was initially a lowering in testosterone levels to a castration level. In the BPH patients, the testosterone levels fluctuated at subnormal levels. None of the patients had testosterone levels which reached castration values during the last three weeks of the treatment. There was a distinct decrease of the symptoms of dysuria and also the prostate volume. In the prostate carcinoma patients, the testosterone values were measured again at the castration levels

at the end of the 6 weeks of therapy along with a considerable improvement in the overall condition of the patient.

The potential suitability of LHRH antagonists, including Cetrorelix, for treating BPH appears in a review article appearing in Arch.-Pharmakol. 350, Suppl., R16, 1994 (Romeis, Ochs, Borbe). In vitro bonding of Cetrorelix to LHRH receptors on the pituitary gland of swine is mentioned. Also mentioned are other possible clinical areas of application, including hormone-dependent tumors.

A comparative survey of the endocrine therapy of BPH in conjunction with 5- α -reductase inhibitors, aromatase inhibitors and anti-androgens is presented in Urology, 1994, 43, 22 suppl. (7-16). However, only LHRH agonists are described.

An overriding disadvantage of known preparations and methods is that the patient usually experiences a sharp drop in testosterone levels along with its associated side effects. In addition, known preparations have only a relatively short term effect. The prostate volume rises once administration stops. An effective therapy scheme for the treatment of BPH with Cetrorelix has not been established.

SUMMARY OF THE INVENTION:

The disclosed invention is directed to a long-lasting therapeutic agent having few side effects for the treatment of both BPH and prostate cancer

The problems existing with the treatments described above are solved by administering the LHRH antagonist Cetrorelix alone or in combination with α -blockers or 5- α -reductase inhibitors such as Finasterides. Preferably, Cetrorelix was administered intermittently according to a specified therapy scheme.

It is also possible with the LHRH antagonist Cetrorelix to determine the extent of a testosterone suppression via the level of the applied dose and also to compensate for it

BRIEF DESCRIPTION OF THE DRAWINGS:

Figure 1 is a summary of the clinical results for specific Cetrorelix dosage regimens PLA refers to a placebo;

Figure 2 (a) shows the effect of the C01 and C10 treatments on prostate size. PLA refers to a placebo;

TREATMENTS: C01 refers to a dosage regimen of 1 mg/day s.c. for 28 days and a 3 months follow-up observation period. C10 refers to a dosage regimen of 10 mg/day for the first one to five days followed by a dosage regime of 1 mg/day s.c. for 28 days and a 3 months follow-up observation period.

Figure 2 (b) illustrates the absolute changes in prostate size from baseline for the C01 and C10;

Figure 3 (a) shows the number of patients with an I-PSS improvement $\geq 40\%$ and also with an improvement $\geq 30\%$ resulting from the treatment C01 and C10 (defined above) PLA is the placebo. I-PSS (International Prostate Symptom Score) includes the following indicia of 1) feeling of incomplete voiding, 2) increased frequency of voiding, 3) dribbling, 4) difficulties to postpone voiding 5) weak urinary stream 6) increased effort to start voiding and 7) nycturia.

Figure 3 (b) shows the I-PSS improvement with the C10 and C01 treatments (defined above) over 120 days, including the observational follow-up period.

Figure 4 (a) shows the improvement in maximum uroflow ≥ 3 ml/sec C10 and C01 (defined above) treatment phases PLA is the placebo; and

Figure 4 (b) shows the rate of uroflow as a function of the C01 and C10 treatments (defined above) over a 120 day period.

DESCRIPTION OF THE PREFERRED EMBODIMENTS:

The invention will be explained in detail using the following clinical results:

EXAMPLESExample 1

Cetrorelix is administered in a dose of 0.5 mg to 2 mg daily for 4 to 8 weeks for the therapy of BPH. A dose of 5 mg to 30 mg, dispensed once per week or every 10 days also over a time period of 4 to 8 weeks as well as one every two weeks or one injection per month of 20 mg to 60 mg can also decisively improve the clinical symptoms and signs. Submaximal decreases of testosterone occur, but these are above those levels associated with castration. The prostate volume decreases by 20 to 40 % during the treatment time of 4 to 8 weeks. An increase of the peak flow of approximately 3 ml/sec of the urine, comparable to the α -blockers, is also achieved with this therapy regimen. In addition, at least 30 % of the patients achieve an improvement of the urine flow of 6 ml/sec with this therapy. This is almost equivalent to an improvement like that associated with the golden standard operation, and in considerably shorter time. No limitations in sexual performance are observed. There are also significant improvements as regards quality of life. These clinical benefits continue for at least 3 to 6 months after therapy. This allows a long-term therapy of BPH with only an intermittent treatment of 2 to max. 4 injection cycles over 4 to 8 weeks.

This therapy represents a significant therapeutic advance in the treatment of BPH since it not only achieves an improvement

of the clinical symptoms of BPH but also a diminution of the prostate and an improvement of the urine flow like those associated with surgery. The protocols of the invention avoid the negative consequences of an operation, e.g. urine incontinence, retrograde ejaculation, blood loss with the consequence of blood transfusions and also the risks of infection associated with surgery.

Example 2

Cetrorelix is administered with α -reductase inhibitors or α -receptor blocking agents to a patient as follows:

For 1 to 12 weeks, Cetrorelix is administered to the patient followed by a 1-12 week period where an α -reductase inhibitor of 5 mg/day, an α -receptor blocking agent in the dose range of 2 mg to 10 mg/day or of 0.1 mg to 0.4 mg/day dependent on each agent or a drug of natural origin 1-6 capsules or tablets/day used for the treatment of BPH is administered. Alternatively, Cetrorelix can be administered for a 1 to 12 weeks period followed by retreatment with Cetrorelix after one to six months.

In summary, it can be readily seen that treatment of BPH with a specific therapy regime involving Cetrorelix or especially a combination of Cetrorelix with 5α -reductase inhibitors or α -blockers such as Naftopidil has decided benefits which occur quickly and are long-lasting.

An effective and economic therapy of this widespread disease can be achieved therewith, which is of extraordinary social and economic significance.

We claim:

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1. A regime for the therapeutic management of benign prostatic hyperplasia and prostatic cancer in a mammalian organism without testosterone levels being in castration range comprising the administration a LH-RH antagonist alone or in combination with α - reductase inhibitors or α -receptor blocking agents according to a regime wherein the LH-RH antagonist is administered over time and in an amount sufficient to reduce the volume of the prostate, BPH symptoms and / or prostate specific antigen levels, without the side effects associated with testosterone levels being in a castration range.

2. The regime according to claim 1 which involves the administration of Cetrorelix as LH-RH antagonist at dosages between 0.5 mg/day and 20 mg/week or about 0.007 mg/kg body weight per day to 0.30 mg/kg body weight per week.

3. The regime according to claim 1 wherein the dosage amount is at levels about 20 to 120 mg Cetrorelix per month or about 0.285 mg/kg to 1.71 mg/kg per month for one to six months, preferably one to three months.

4. The treatment according to claim 1 or 3 wherein Cetrorelix is administered with α -reductase inhibitors or α -receptor blocking agents in a specific timely regime.

5. The treatment according to claim 1 or 3 wherein the timely regime is as follows:

1 to 12 weeks of Cetrorelix treatment followed by 1 to 12 week treatment with an 5 α -reductase inhibitor or an α -receptor blocking agent or any drug of natural origin used for the treatment of BPH or alternatively, 1 to 12 weeks of Cetrorelix treatment followed by
5. retreatment with Cetrorelix after six months.

6. The treatment according to claim 5 wherein the regime is as follows:

1 to 12 weeks of Cetrorelix treatment followed by 1 to 12 weeks treatment with an 5 α -reductase inhibitor or an α -receptor blocking agent or any drug of natural origin used for the
10. treatment of BPH or alternatively, 1 to 12 weeks of Cetrorelix treatment followed by continuous treatment of a 5 α - reductase inhibitor or a α -receptor blocking agent and retreatment with Cetrorelix after six months.

7. A regime for the therapeutic management of prostatic cancer in a mammalian organism
15. without testosterone levels being in a castration range according to claim 1 comprising the administration about 0.5 to 5 mg per day Cetrorelix as LH-RH antagonist for 1 to 12 weeks continuously or intermittently alone or together with a 5 α - reductase inhibitor or α -receptor blocking agent and optionally followed by retreatment with Cetrorelix alone or in the a.m. combination after six months.

Figure 1

Cetorelix

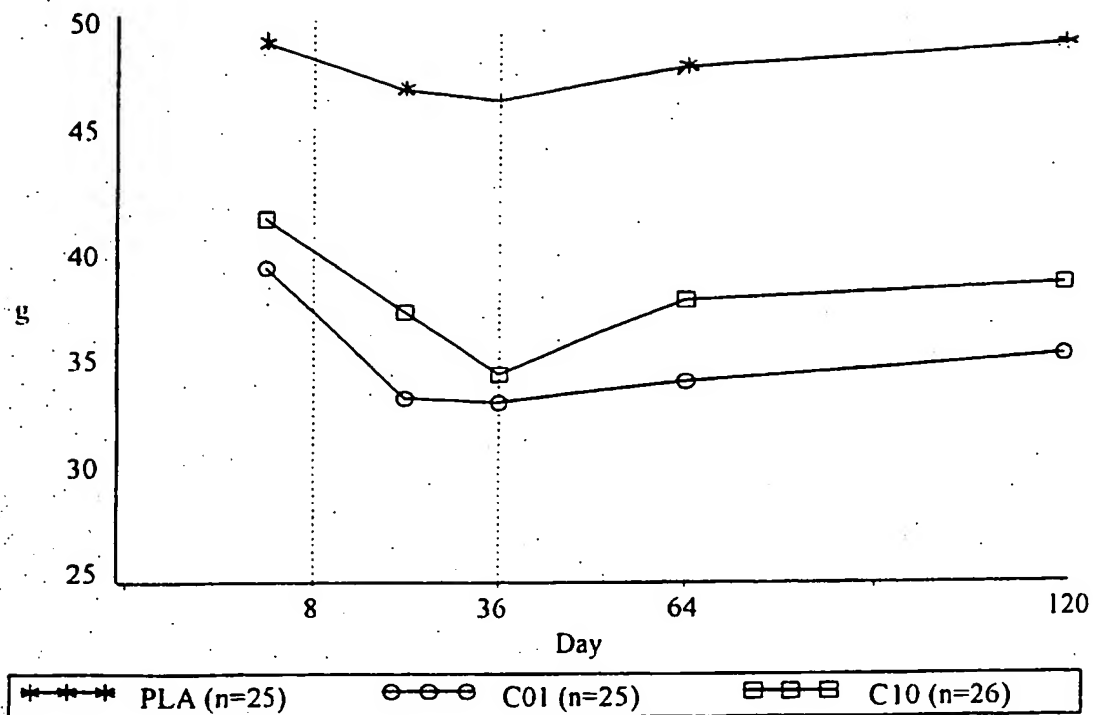
Development Indication BPH

Indication	Subj. Nos.	Result	Phase	Salt *	Dose/Day (mg)	Posology (days)
BPH	11/11	Relief of symptoms Decrease of prostate vol. No castration	I/II a	1	0.5 bid	28
BPH	7/7 7/7	Relief of symptoms Decrease of prostate vol. independent from extent of hormonal suppression	I/II a	1 2	10(d1) + 1 (d2-28) 30(d1) + 30(d8)	28 28
BPH (not operable)	15/10		II	1	5bid(d1+2)+ 1od (d2-56)	56
BPH	84/78 (79) /27 /25 /26	<u>Obj.:</u> ↓ IPSS ↓ prostate volume ↓ hormones, incl. DHT dose dependent efficacy castration level not necessary long lasting effects ≥ 3 month after treatment termination	II	1	Pla run-in 10(d8-13) + 1(d-35) 1(d8-35) Pla(d8-35)	28 + 7d Pla run-in
Sum finish	114 pat.					

* 1 = Cetorelix Acetate (Lyophilisate) 2 = Cetorelix Pamoate

Figure 2(a)

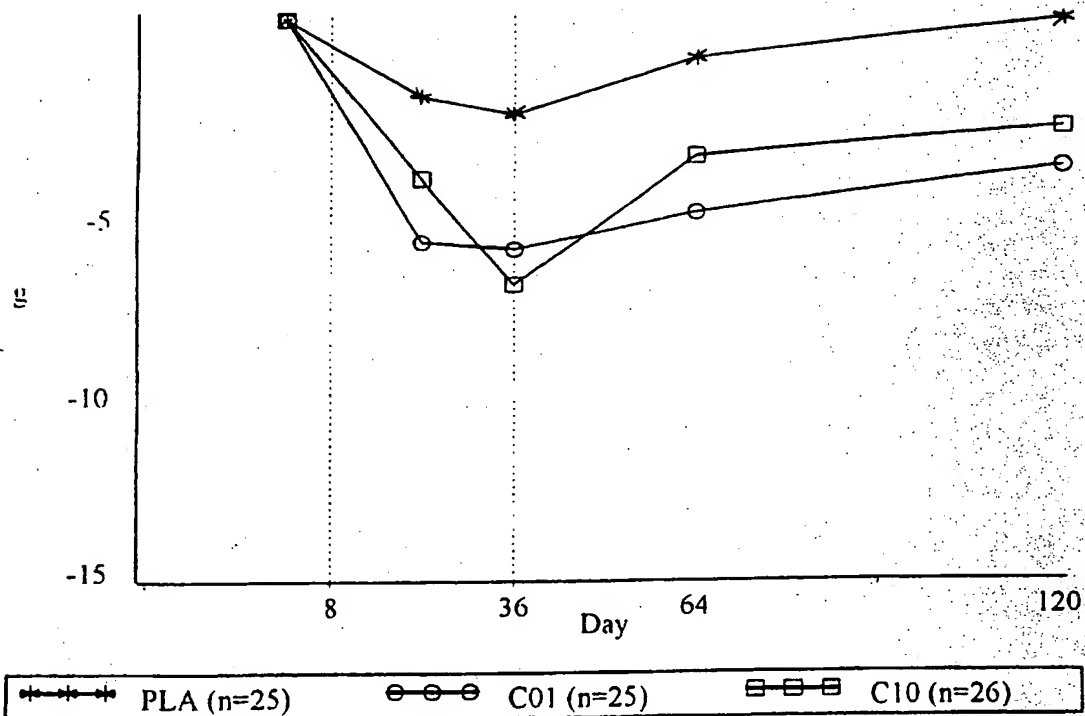
Prostate size - Means



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Figure 2(b)

Prostate size - Mean absolute changes from baseline



Rate of patients with an I-PSS improvement $\geq 40\%$
Per protocol analysis

Cetrorelix Acctate

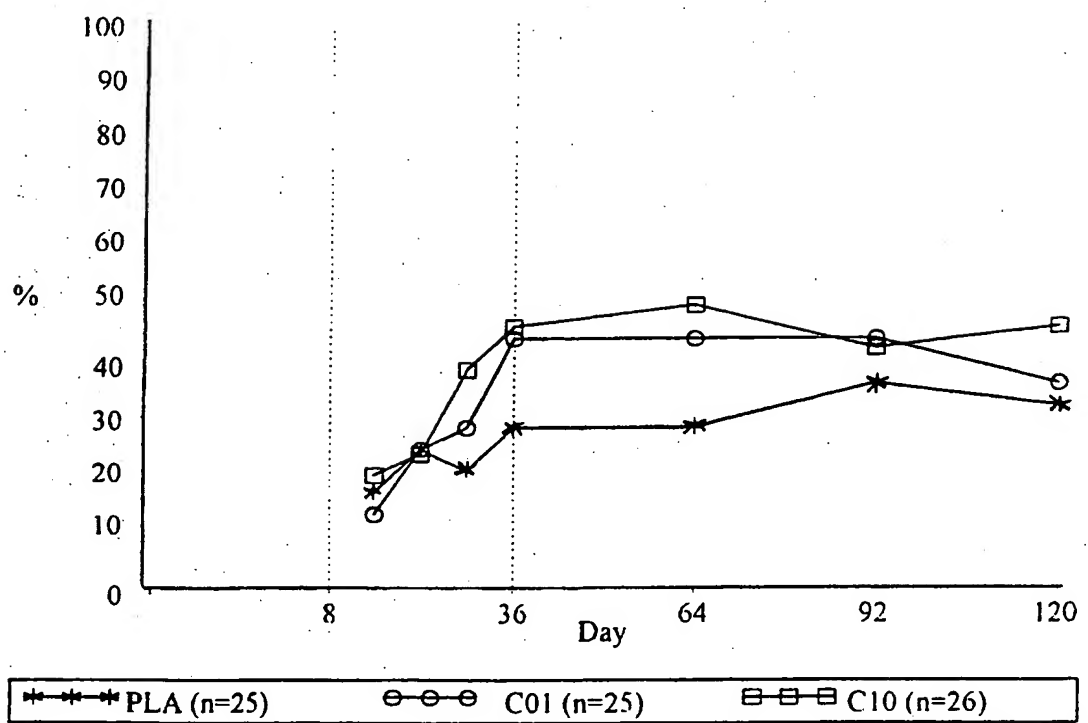
Treatment	$\geq 40\%$ Resp.			$\geq 30\%$ Resp.
		Pt. no.	Pt. %	% Pt.
PLA	no	18		
	yes	17	28	32
C01	no	14		
	yes	11	44	52
C10	no	14		
	yes	12	46	53.8

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Figure 3(b)

Rate of patients with an I-PSS improvement $\geq 40\%$
Per protocol analysis

Cetrorelix Acetate

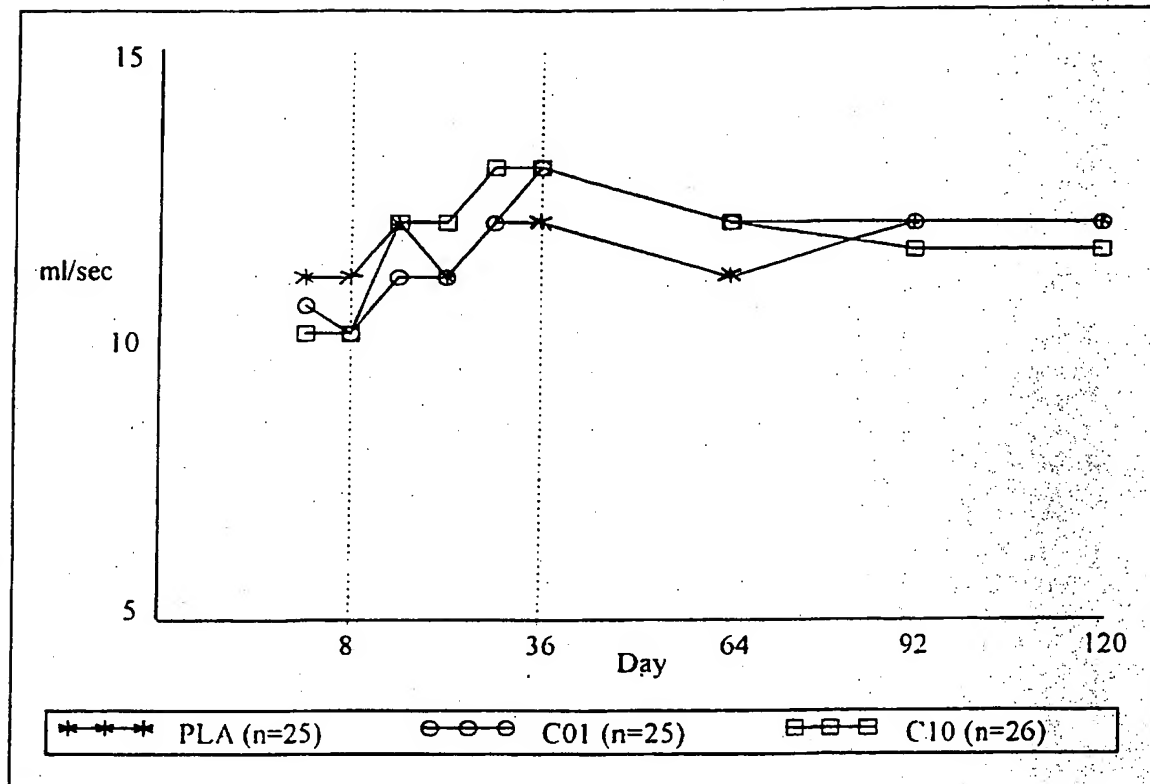


Improvement of maximum uroflow ≥ 3 ml/sec at end of treatment phase per protocol analysis

Treatment	Improvement ≥ 3 ml/sec					
	no		yes		TOTAL	
	No.	%	No.	%	No.	%
PLA	13	52.0	12	48.0	25	100.0
C01	12	48.0	13	52.0	25	100.0
C16	16	61.5	10	38.5	26	100.0

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Figure 4(b)



Maximum urinary flow rate - medians

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/04740

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/09 //(A61K38/09,31:495)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GONZALEZ-BARCENA ET AL: "RESPONSES TO THE ANTAGONISTIC ANALOG OF LH-RH (SB-75, CETROLIX) IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA AND PROSTATIC CANCER" THE PROSTATE, vol. 24, 1994, pages 84-92, XP002054664 cited in the application see the whole document and note particularly comments at page 87, paragraph 2, and figure 4 --- -/-	1-3,5,7

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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Date of the actual completion of the international search

5 February 1998

Date of mailing of the international search report

23.02.98

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Sitch, W

INTERNATIONAL SEARCH REPORT

Intern. Appl. No.

PCT/EP 97/04740

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>OESTERLING: "ENDOCRINE THERAPIES FOR SYMPTOMATIC BENIGN PROSTATIC HYPERPLASIA" SUPPLEMENT TO UROLOGY, vol. 43, no. 2, 1994, pages 7-16, XP002054665 cited in the application see the whole document</p> <p>----</p>	
A	<p>GB 2 218 335 A (INNOFINANCE ALTALANOS INNOVACI) 15 November 1989 see page 5, paragraph 1 - page 11, paragraph 4</p> <p>-----</p>	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 97/04740

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a):

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 1-7
are directed to a method of treatment of
the human/animal body , the search has been carried out and based on the
alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Appl. No.

PCT/EP 97/04740

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2218335 A	15-11-89	BE 1004932 A	02-03-93
		CH 678013 A	31-07-91
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		SE 8901660 A	11-11-89

Form PCT/ISA/210 (patent family annex) (July 1992)

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